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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,474	08/04/2000	HANNSJORG SINN	8484-077-999	6359

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,474	SINN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,15,16 and 18* is/are pending in the application.

4a) Of the above claim(s) *4,7,9 and 18* is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1,5,8,10 and 16* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 10/31/03, claims 1, 5, 8, 10, 15, 16 have been amended, and claims 2 and 13 cancelled. Claims 1, 4-10, 15, 16, 18 remain pending. Claims 4, 7, 9, 18 remain withdrawn from consideration, since these claims do not encompass the elected specie. Claims 1, 5-6, 8, 10, 15, 16 are examined in this Office action. Applicants' arguments filed 10/31/03 have been considered and found persuasive in part. The rejection of claim 1 over Tryggvason ('058) is withdrawn.

Claim 6 is objected to because of its dependence on a rejected claim. Claim 15 is characterized as allowable at the present time.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5, 8, 10, 16 are rejected under 35 U.S.C. §102(e) as being anticipated by

Scherz (USP 5,650,292).

Scherz discloses (col 6, line 58; col 8, line 32) porphyrin conjugates of proteins (containing an amide linkage) which localize in tumors. Pharmaceutical compositions are also disclosed.

Thus, the claims are anticipated.

*

Claims 1, 5 and 10 are rejected under 35 U.S.C. §102(b) as being anticipated by Fernandez (USP 4,923,819).

Fernandez discloses (col 9, line 41+) a conjugate of human albumin and a fluorescent group, wherein the fluorescent group is bonded to the albumin via amide linkage. Also disclosed (col 9, line 22+) is a conjugate between dimethylamino naphthalenesulfonic acid and bovine albumin.

The property of being useful for distinguishing cancerous or inflamed tissue is inherent in the conjugate. Thus, the claims are anticipated.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 1 is are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over Carlsson (USP 4,231,999).

As indicated previously, Carlsson discloses (col 15, line 46 to col 16, line 15) a method for preparing a conjugate of albumin in which fluorescein is bonded via a linker to albumin.

The conjugate can be represented as follows:

Fluor-GSH-L-albumin

wherein "Fluor" represents fluorescein, "GSH" represents glutathione, and "L" represents the following linking moiety: $-S-CH_2-CH_2-CO-$. The moiety "Fluor-GSH-L-" is bonded to albumin via an amide linkage.

The response argues that the disulfide bond of the Carlsson conjugate will be reduced by the action of (reduced) glutathione (abbreviated "GSH"). In support of this assertion, the response points to a passage from a biology textbook which states that:

> "cytosolic proteins in... eukaryotic cells do not utilize the disulfide bond a stabilizing force because the high GSH/GSSH ration would [reduce the disulfide bonds]".

However, albumin is not a cytosolic protein. Further, a substantial portion of all known proteins in humans contain disulfide bonds that remain intact despite the presence of GSH in the cytosol. For example, human albumin itself contains 17 disulfide bonds which "contribute to the high stability of the albumin molecule" (see Konig, USP 4,990,447, col 1, line 17). Further, it is not evident that the conjugate must enter the cytosol in order to "distinguish cancerous tissue from healthy tissue", but even if the conjugate enters the cytosol and becomes reduced, the fluorescent group will still be present. Thus, the passage from Lodish ("Molecular Cell Biology", 1999) provides neither direct evidence nor indirect evidence that the disulfide bond of the Carlsson conjugate will be unstable in serum, or that the Carlsson conjugate will fail to "distinguish cancerous tissue from healthy tissue".

The rejection is maintained.

*

Claim 5 is rejected under 35 U.S.C. §103 as being unpatentable over Tryggvason (USP 4,677,058).

As indicated previously, Tryggvason discloses (col 4, lines 13-24) that fluorescein-conjugated anti-rabbit IgG could be used to detect the presence of malignant tumor cells. The fluorescein conjugate was prepared by reacting the isothiocyanate of fluorescein (FITC) with immunoglobulin G. The reference does not disclose that the fluorescent moiety was

bonded to the IgG by an amide linkage. Claim 5 requires that the fluorescent moiety is bonded to the carrier protein by an amide linkage. Reaction of an aryl isothiocyanate (such as FITC) with a protein that contains lysine groups results in a thiourea bond, not an amide bond. However, the lysine which bears the fluorescein moiety is itself bonded, via amide linkage, to the remainder of the protein. Claim 5 does not impose any limitations on the structure of the "fluorescent moiety". The "fluorescent moiety", therefor, could be a fluorescein conjugated to a single lysine.

The response argues that claim 1 should not be rejected. Claim 1 is not now rejected. Claim 5 is rejected, since fluorescein contains two hydroxyl groups. Thus, it would have been obvious to one of ordinary skill that when the "fluorescent moiety" is fluorescein conjugated to a single lysine, the fluorescent moiety is bonded via amide linkage to a carrier protein.

*

Claims 5, 8, 10, 16 are rejected under 35 U.S.C. §103 as being unpatentable over Lavallee (USP 4,783,529).

Lavallee discloses (col 2, line 30; col 2, line 49-54) conjugates for tumor imaging. The conjugates comprise porphyrins; the porphyrins can be conjugated (col 11, line 51+) to immunoglobulins. Many of the porphyrins bear acidic groups (i.e., carboxylic and or sulfonic acid). Lavallee does not recite the phrase "distinguish cancerous tissue from

healthy tissue".

Lavallee is focused primarily on the preparation of porphyrins and their conjugation to carrier proteins such as antibodies, and is less concerned with experimental specifics of immunochemical methods of detecting tumor cells. However, the suggestion to use the immunoconjutes for detecting tumor cells is certainly present in the reference, and the immunochemist of ordinary skill is acquainted with methods of using antibodies to detect tumor cells. In particular, the immunochemist of ordinary skill would expect that for a diagnostic imaging method to be successful, the conjugate employed would be effective to "distinguish cancerous tissue from healthy tissue". Accordingly, the claims are rendered obvious.

*

Claim 1 is rejected under 35 U.S.C. §103 as being unpatentable over Scherz (USP 5,650,292).

As indicated above, Scherz discloses (col 6, line 58; col 8, line 32) porphyrin conjugates of proteins which localize in tumors. In particular, Scherz discloses (col 19, line 38+) a bovine albumin conjugate of a porphyrin, wherein the porphyrin is bonded to the protein via an amide bond. Scherz does not disclose that human albumin should be substituted for the bovine albumin. However, the artisan (of ordinary skill) endeavoring to administer the conjugates to humans, rather than cows, would have been motivated to use

the human protein, e.g., to reduce antigenicity.

*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner an normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 2/10/04

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